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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/886,400	06/20/2001	Dennis Murphy	DIVER1120-4	4902

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EXAMINER	
RAMIREZ, DELIA M	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 07/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/886,400	MURPHY ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *93-95,99-121,125-132 and 138-152* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *104,132,151-152* is/are allowed.

6)☒ Claim(s) *93-94,99-102,105-120,125-127,129-131,138-150* is/are rejected.

7)☒ Claim(s) *95,103,121,128* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Claims 93-95, 99-121, 125-132 and 138-152 are pending.

Applicant's amendment of claims 93, 95, 99-103, 105-119, 121, 125-132, and addition of claims 138-152, in a communication filed on 5/19/2004 are acknowledged.

Applicant's submission of a declaration by inventor Jay Short under 37 CFR 1.132 in a communication filed on 6/11/2004 is acknowledged.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 112, Second Paragraph

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 149 and 150 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

3. Claim 149 is indefinite in the recitation of "polypeptide comprising an active fragment of the polypeptide of claim 93" as it is unclear what the meaning of the term "active fragment" is within the context of the claim. As written, one cannot determine if the term "active" refers to "α-galactosidase activity" or if another "activity" is being implied, such as the ability to elicit antibodies. For examination purposes, no patentable weight will be given to the term. Correction is required.

4. Claim 150 is indefinite in the recitation of "polypeptide is associated with a polyethylene glycol" as it is unclear and confusing. As written, it is unclear if the "association" refers to chemical linkage of the claimed polypeptide to polyethylene glycol or if the "association" refers to an undefined relationship

between the claimed polypeptide and polyethylene glycol. For examination purposes, it will be assumed that the term reads "polypeptide is chemically linked to polyethylene glycol". Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. Claims 105-115, 129-131 remain rejected and newly added claims 138-149 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection has been discussed at length in previous Office Actions mailed on 6/18/2002, 3/26/2003 and 12/19/2003.

7. Applicants argue that the claimed invention is adequately described in the specification. Applicants submit that the amendment as filed addresses the issue of functional limitation in the claims. Applicants also indicate that the claims now read on a genus of polypeptides having 70% sequence identity to the exemplary sequence or being encoded by a nucleic acid having at least 70% sequence identity to the exemplary sequence. Applicants further refer to the USPTO written description guidelines and point the Examiner's attention to Example 14 (Exhibit A). Applicants submit that procedures for making the variants in that example are known in the art and that in Example 14, there is no disclosure as to which structural features or elements in the exemplary polypeptide have the catalytic activity and can be modified such that the claimed genus in Example 14 can have the same activity. Therefore, it is Applicant's contention that the claimed invention meets the written description requirements for the same reasons indicated in Example 14 of the guidelines. According to Applicants, the claimed genus of polypeptides is described by structure and function.

8. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection of claims 105-115, 129-131 or avoid the rejection of claims 138-149. The Examiner acknowledges amendments to the claims in regard to a functional limitation, however it is noted that claim 149 is directed to a genus of polypeptides comprising any fragment of the polypeptide of claim 93 and no functional limitation has been recited for the claimed genus. Furthermore, while the Examiner acknowledges Example 14 of the guidelines, the Examiner disagrees with Applicant's contention that the cited example is analogous to the instant case. As repeatedly indicated in previous Office Actions, a sufficient written description of a genus of polypeptides may be achieved by a recitation of a representative number of polypeptides defined by an amino acid sequence or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. While 95% sequence identity can be considered to be a substantial portion of the genus since only 5% of the structure is variable, as indicated in Example 14, the instant claims do not recite a representative number of species nor do they recite structural features which one of skill in the art would consider a substantial portion of the genus. Claims 105-115, 131 and 138-148 are directed to a genus of polypeptides having α-galactosidase activity wherein said polypeptides comprise fragments ranging from 10-150 consecutive amino acids of SEQ ID NO: 4 or 10-150 amino acids of a polypeptide having at least 70% sequence identity to SEQ ID NO: 4. Therefore, at best, the structural elements recited constitute between 2.7% up to 41% of the total structure of the polypeptide of SEQ ID NO: 4 (364 amino acids; 41%=150x100/364; 2.7%=10x100/364). In the case of claims 138-148, the structural elements shared constitute less than the range indicated above (2.7%-41% of the structure of SEQ ID NO: 4) in view of the fact that these structural elements are derived from a polypeptide having 70% sequence identity to SEQ ID NO: 4. Similarly, the structural element recited in claim 149, i.e. any fragment of the polypeptide of SEQ ID NO: 4, is not considered a substantial portion of the genus since SEQ ID NO: 4 is 364 amino acids long and a fragment of SEQ ID NO: 4 can have anywhere between 2 and 363 amino

acids. With regard to claims 129-130, the structural limitation recited, i.e. any number of conservative substitutions in the polypeptide of SEQ ID NO: 4, is not deemed to encompass a substantial portion of the genus in view of the fact that this genus encompass species which would have little or no structural elements in common with the polypeptide of SEQ ID NO: 4. Any amino acid in the polypeptide of SEQ ID NO: 4 can be conservatively substituted for another amino acid. In view of the structural elements recited in the claims, it is unclear as to how one of skill in the art can reasonably conclude that the claimed genus is analogous to that in Example 14 of the guidelines or that the specification adequately describes the claimed invention.

9. Claims 93-94, 99-102, 105-120, 125-127, 129-131 remain rejected and newly added claims 138-149 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polypeptide comprising SEQ ID NO: 4, does not reasonably provide enablement for (1) polypeptides having α-galactosidase activity wherein said polypeptides are at least 70%, 75%, 80%, 85%, 90% sequence identical to the polypeptide of SEQ ID NO: 4, (2) polypeptides having α-galactosidase activity comprising fragments of the polypeptide of SEQ ID NO: 4 or comprising fragments of a polypeptide having at least 70% sequence identity to SEQ ID NO: 4, (3) polypeptides which catalyze the enzymatic hydrolysis of saccharides or have α-galactosidase activity and are encoded by polynucleotides having at least 70%, 75%, 80%, 85% sequence identity to SEQ ID NO: 3, (4) polypeptides having α-galactosidase activity which result from conservatively substituting any number of amino acids in the polypeptide of SEQ ID NO: 4, or (5) polypeptides of any function comprising any fragment of the polypeptide of SEQ ID NO: 4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This rejection has been discussed at length in previous Office Actions mailed on 6/18/2002, 3/26/2003 and 12/19/2003.

10. Applicants argue that the claims as amended now recite a functional limitation and that they read on a genus of polypeptides having 70% sequence identity to the exemplary sequence or being encoded by nucleic acids having 70% sequence identity to the exemplary sequence. Applicants refer to a declaration by inventor Jay Short and indicate that in that declaration, Dr. Short states that the state of the art at the time of the invention and the level of skill of the person of ordinary skill in the art was very high in regard to screening enzymes and nucleic acids encoding enzymes having α-galactosidase activity. Applicants submit that Dr. Short declares that the creation of variants would not have required any knowledge or guidance as to which specific structural elements correlate with α-galactosidase activity. Applicants further point out that Dr. Short declares that methods known at the time of the invention for modifying nucleic acids or proteins in combination with high throughput enzyme activity screening made knowledge of protein structure obsolete. Applicants submit that enablement is not precluded by the need to screen large number of compounds as long as that screening is routine, and state that the declaration clearly indicate that making the variants recited in the claims would require the use of routine protocols.

11. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection of claims 93-94, 99-102, 105-120, 125-127, 129-131 or avoid the rejections of newly added claims 138-149. The Examiner acknowledges the declaration by Dr. Short and the amendments made to the claims. However, the Examiner disagrees with Applicant's contention that the specification fully enables the full scope of the claimed invention. Claims 93-94, 99-102, 118-119 are directed to polypeptides having α-galactosidase activity wherein said polypeptides are at least 70%, 75%, 80%, 85%, 90% sequence identical to the polypeptide of SEQ ID NO: 4. Claims 105-115, 131 and 138-148 are directed to polypeptides having α-galactosidase activity comprising fragments of the polypeptide of SEQ ID NO: 4 or comprising fragments of a polypeptide having at least 70% sequence identity to SEQ ID NO: 4. Claims 116-117, 125-127 are directed to polypeptides which catalyze the enzymatic hydrolysis of saccharides or have α-galactosidase activity and are encoded by polynucleotides having at least 70%,

75%, 80%, 85% sequence identity to SEQ ID NO: 3. Claim 120 is directed to the polypeptides of claim 116 with the added limitation that the polypeptides renature and regain α-galactosidase activity after exposure to temperatures ranging between 60 C to 105 C. Claims 129-130 are directed to polypeptides having α-galactosidase activity which result from conservatively substituting any number of amino acids in the polypeptide of SEQ ID NO: 4. Claim 149 is directed to polypeptides of any function comprising any fragment of the polypeptide of SEQ ID NO: 4. The scope of the claims is not commensurate with the enablement provided in regard to the large number of proteins of unknown function encompassed by the claims, as well as the lack of knowledge in regard to the structural elements required in the claimed polypeptides such that they display the desired activity. As repeatedly indicated in previous Office Actions, the specification while disclosing the structure of the polypeptide of SEQ ID NO: 4 and that of the corresponding polynucleotide, i.e. SEQ ID NO: 3, fails to disclose the structural elements in SEQ ID NO: 3 or 4 or fragments thereof which correlate with the desired activity. There is no clue as to which are the critical structural elements required in addition to those fragments of the polypeptide of SEQ ID NO: 4 recited such that the claimed polypeptides display α-galactosidase activity. There is no teaching or suggestion as to which are the structural elements in the polypeptide of SEQ ID NO: 4 responsible for renaturing or regaining α-galactosidase activity after exposure to temperatures ranging from 60 C to 105 C. It is reiterated herein that the art as previously discussed teaches that even minor structural changes can result in major changes in function. See the teachings of Broun et al., Van de Loo et al., Seffernick et al. and Witkowski et al. previously presented. Thus, in the absence of some teaching or suggestion as to how structure correlates with the desired function, one of skill in the art would have to go through the burden of undue experimentation to practice the full scope of the claimed invention.

The Examiner agrees with Applicant's contention that enablement is not precluded by the need of screening a reasonable number of compositions as long as that screening is routine, and that many methods were known in the art at the time of filing regarding the creation of nucleic acid and polypeptide

variants. However, the Examiner disagrees with Applicant's contention that practicing the claimed invention would not constitute undue experimentation. Testing the extremely large number of variants encompassed by the claims when there is no guidance or knowledge as to which are the structural elements in the polypeptide of SEQ ID NO: 4 which correlate with the desired activity, i.e. α-galactosidase activity, enzymatic hydrolysis of any saccharide, or renaturation/regaining of α-galactosidase activity after exposure to temperatures ranging from 60-105 C, would constitute undue experimentation in view of the fact that it is not routine in the art to create an infinite number of variants and test them for activity. Instead, one of skill in the art would require some knowledge or guidance as to how structure correlates with function such that a reasonable number of variants with the potentiality of having the desired function can be created and tested. Thus, in view of the information provided, the lack of relevant examples, the lack of knowledge as to which structural elements in the polypeptide of SEQ ID NO: 4 correlate with the desired function, and the unpredictability of the art regarding functional annotation based solely on structural homology, one of skill in the art cannot reasonably conclude that the specification enables the full scope of the claimed invention.

Allowable Subject Matter

12. Claims 104, 132, 151-152 appear to be allowable over the prior art of record.

13. Claims 95, 103, 121, 128 appear to be allowable over the prior art of record but are objected to since they depend upon rejected base claims.

Conclusion

14. No claim is in condition for allowance.

15. Applicant's amendment of claims 93, 95, 99-103, 105-119, 121, 125-132 and addition of claims 138-152 necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS**

ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 872-9306. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

17. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or

relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
July 15, 2004

REBECCA E. PROUTY
PRIMARY EXAMINER
~~C.T.A.U. 1200~~
1652